

4-Tesla High Angular Resolution Diffusion Tractography Analysis of the Human Connectome in 234 Subjects: Sex Differences and EPI Distortion Effects

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Introduction:

Cortical fiber connectivity, assessed with diffusion-based tractography, has great potential for investigating how the normal and diseased brains are organized. Connectivity patterns may differ between men and women, contributing to sex differences in linguistic processing [1] and general cognition [2]. Yan et al. [3] found sex differences in cortical connectivity in the precuneus and orbito-frontal regions, using DTI tractography in 72 subjects. Using DSI-based tractography, in 5 subjects, Hagmann et al. [4] examined cortical network connectivity. DWI is susceptible to EPI-induced artifacts due to magnetic field inhomogeneities at air-tissue interfaces, particularly at high magnetic field strengths. For this reason, accurate intrasubject registration is vital when merging anatomical and diffusion MRI. In one of the largest-ever HARDI tractography studies, we analyzed cortical connectivity in 234 young adults. We discovered sex differences in regional connection densities. EPI distortion correction also affected the results.

Methods:

We scanned 234 young adult twins (147 women/87 men; mean age: 23.4 ± 2.0 SD years) with 4T HARDI and T1-weighted structural MRI. From skull-stripped images, we extracted 35 regions of interest per hemisphere (70 per brain) on cortical surface models reconstructed using FreeSurfer software. All T1-weighted images were linearly aligned (9 DOF) to a common space. DWIs were corrected for eddy current distortions using FSL software. For each subject, the b_0 images were averaged, aligned, and resampled to a downsampled version of their corresponding T1 image. To compensate for EPI-induced susceptibility artifacts, these b_0 maps were registered to the sMRI using inverse-consistent elastic image registration [5]. Constant solid angle orientation distribution functions (CSA-ODFs) were computed [6]. A novel Hough transform based tractography method was performed using these ODFs by probabilistically seeding voxels [7]. Normalized counts of fibers passing through and between each ROI were used to create connectivity matrices for each subject. We analyzed sex differences using random effects regression to account for kinship between subjects.

Results & Discussion:

Corrected and uncorrected connectivity matrices were significantly different ($p=0.0094$), based on a paired t-test in regions with detected connections in corrected data. Sex differences were examined in both sets of connectivity matrices. Consistent with prior findings on cortical sex differences [3,7], fiber counts in the right lateral orbito-frontal cortex were higher for women in both cases ($p_{EPIcor} = 7.5 \times 10^{-5}$, $p_{noEPIcor} =$

1.3×10^{-4}) after Bonferroni correction for multiple comparisons. additional regions were identified as significantly different between sexes when correction was not performed—those between the right insula and right lateral orbito-frontal cortex ($p_{noEPIcor} = 1.0 \times 10^{-4}$), and those that pass through the right inferior temporal lobe ($p_{noEPIcor} = 1.3 \times 10^{-4}$). In conclusion, images must be nonlinearly co-registered, to minimize false discoveries when studying factors that influence the human connectome.

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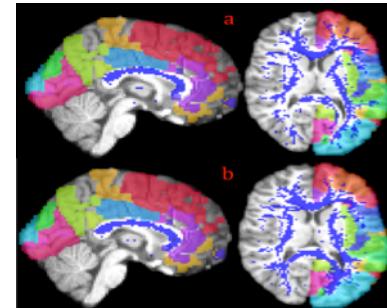


Fig. 1. Binarized fiber density maps (blue) of the same individual computed before (a) and after EPI distortion correction (b), overlaid on the structural image, with cortical regions extracted.

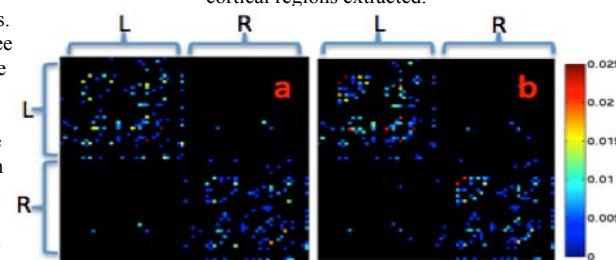


Fig. 2. Network analysis was used to create matrices describing the average proportion of fibers connecting different cortical regions, before (a) and after (b) EPI distortion correction. A greater degree of connections are seen within a hemisphere than across hemispheres. In general connections are stronger (redder colors as opposed to bluer) after correction than before. On average, about 65% of the total number of fibers traced crossed at least one cortical region before EPI correction, while 75% crossed afterwards.